**Original Research Article**

# Compliance and tolerability evaluation of diacerein versus s-adenosyl methionine in osteoarthritis patients

**Gayathri C.R.[1*], Vanitha Samuel[2], Senthilnathan A[3], Nirmala P[4]**

[1]Post Graduate, Department of Pharmacology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India
[2]Professor, Department of Pharmacology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India
[3]Professor, Department of Orthopaedics, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India
[4]Professor and HOD, Department of Pharmacology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India
[*]Corresponding author email: **gay3.gayu23@gmail.com**

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## Abstract

**Background:** Diacerein and S-adenosyl methionine (SAMe) are symptomatic slow-acting drugs in osteoarthritis (SYSADOA). Diacerein is a semisynthetic, anthraquinone derivative, an interleukin 1beta inhibitor with anti-inflammatory, anti-catabolic and pro-anabolic properties on cartilage and synovial membrane. SAMe is a dietary supplement used in the management of OA. The objective of this study is to find out compliance and tolerability evaluation of Diacerein versus S-adenosyl methionine inpatients suffering from Osteoarthritis.

**Materials and methods:** This was a prospective, randomized, interventional study conducted in Orthopedic OPD and ward in Rajah Muthiah Medical College and Hospital for a period of one year. A total of 80 patients were enrolled in this study as per the inclusion criteria. 40 patients in each group were randomly assigned to receive either diacerein 50mg BD or SAMe 200 mg TDS for12 weeks. The NSAID diclofenac 50 mg BD was administered orally for a short course of one week to both the groups to relieve acute symptoms. Efficacy of both the drugs was assessed using Lysholm knee scoring scale. The tolerability profile was evaluated during each clinical visit on weeks 1, 4 and 12.

**Results:** Diacerein and SAMe which were symptomatic slow-acting drugs show a profound reduction in pain starting from 4th to 12th week of treatment. Lower GI side effects like diarrheawere observed in the diacerein group and insomnia was reported in the SAMe group. Though the overall adverse effects were more in the diacerein group, compliance was better with regard to drug intake

**Conclusion:** Both diacerein and SAMe were found to be effective in reducing the pain in Osteoarthritis patients. Diacerein with a good compliance factor was less tolerable because of the incidence of diarrhea. SAMe though better tolerated has a compliance score of fair to good.

## Key words

Diacerein, S-adenosyl methionine, Diclofenac, Osteoarthritis.

## Introduction

The common challenges that most countries face are the delivery of consistent, appropriate and high-quality health care standards within the limits of availableresources. Over the last decade, several scientific societies involvedin OA management produced guidelines for the management ofhip, knee, andhand to improve quality and effectiveness ofpatients care.An epidemiological study of an urban Thai population suggested that the prevalence of symptomatic knee OA in Thailand is 34.5% among persons over 60 years of age [1]. 70% of all osteoarthritis is knee osteoarthritis and the risk for knee increases to 57% in those with a past H/O knee injury. The clinical manifestations include recurring episodes of pain, swelling, synovitis with effusion, stiffness & progressive limitation of motion.

Pharmacological therapies with analgesics and anti-inflammatory drugs form the mainstay of treatment for OA because of their well-established efficacy [2]. Long term use, especially in the elderly produces potentially serious adverse effects. Recently research in newer avenueshas focused on the development of agents which improve the clinical symptoms of OA with better tolerability and safety profiles. Such symptomatic and slow acting drugs for OA (SYSADOA) [3] include Diacerein and S-adenosyl methionine (SAMe).

Diacerein one of the symptomatic slow-acting drugs for OA is a semi-synthetic anthraquinone derivative extracted from certain plants reduces the severity of OA and helpsto modify the course of the disease [4]. It exerts its pharmacological action through its active metabolite-rhein [5]. Besides its anti-inflammatory properties, diacerein has been shown to have anti-catabolic [6] and pro-anabolic [7] effects on cartilage and synovial membrane, as well as protective effects against subchondral bone remodeling.

*S*-Adenosyl-L-methionine (SAMe), first discovered in 1952 [8], is formed from the essential amino acid methionine and adenosine triphosphate. SAMe is found in every living cell, where itfunctions as a donor of methyl groups in >100 different reactions catalyzed by methyl-transferase enzymes. The potential benefit of SAMe in treating osteoarthritis was discovered when patients enrolled in clinical trials of SAMe for depression reported marked improvement in their osteoarthritis symptoms [9]. Experimental studies indicate that SAMe increases chondrocyte proteoglycan synthesis and proliferation rate [10].

In the current shift of understanding of the pathogenesis of osteoarthritis from biomechanical to biochemical, diacerein and SAMe holds a lot of promise in the management of osteoarthritis.

## Materials and methods

### Setting and Selection Criteria

The present study was a prospective, randomized interventional study of subjects with knee OA for a period of 12 weeks. This duration was chosen based on results observed in several studies,

which highlighted a delay of action by both drugs on the signs and symptoms of OA and to evaluate the drug safety, compliance and tolerability profile. This study was carried out in the Orthopaedic outpatient department of Rajah Muthiah Medical College and Hospital, Chidambaram from March 2016 to April 2017. Approval was obtained from Institutional Ethics Committee before initiating the study. A total of 80 patients were enrolled in the study after obtaining informed consent. Diagnosis as primary or secondary OA with unilateral or bilateral knee involvement was done by the Orthopedecian. The clinical criteria for inclusion were adults 40 years or older, occurrence of symptomatic disease with pain present most days or crepitus onmotion. The major criteria for exclusion were evidence of infection, polyarthralgia, rheumatoid arthritis, uncontrolled hypertension, Congestive heart failure, patients on drugs for psychiatric illness. Patients were not retained for the study if they had a serious concomitant medical illness or knee surgery planned within the following 6 months.

**Study Procedure**

Those who gave written consent to participate in the study were randomized into two groups. Forty patients in each group were assigned to receive either Diacerein (50 mg BD) or S-adenosyl methionine (200 mg TDS) daily for 12 weeks along with a short course of diclofenac 50 mg BD given to both groups for one week. All the drugswere administered orally after food intake. Study medications were dispensed once at baseline visit for one week and subsequently at the first follow up visit. Patients returned for assessment after the baseline visit at weeks 1, 4 and 12. Telephone calls at weeks 6 and 8 were made to ensure compliance during the follow-up period. No other systemic or intra-articulardrugs for OA was allowed during the study. The data was recorded in a data sheet containing patient's basic details. Clinical symptoms like pain, duration of the disease, morning stiffness and restricted movements with the final diagnosis was recorded.

**Drugs**

S-adenosyl methionine used in this study was enteric coated 200 mg tablets, marketed by Sun pharma laboratories Ltd. Diacerein capsules equivalent to diacerein IP 50mg manufactured by Glenmark Pharmaceuticals. Both the drugs was purchased from the local pharmacy. Tablet diclofenac 50mg from the hospital pharmacy was prescribed to the patients.

**Evaluation of efficacy**

The primary efficacy parameter was the patient's assessment of pain on movement using Lysholm knee scoring scale with a total score of 100 grading of<65- poor, 65-83- fair, 84-90-good and >90-Excellent. An improvement in score indicates the reduction in pain level. Patients were assessed during each clinical visit at week 0 (baseline), $1^{st}$, $4^{th}$, and $12^{th}$ week.

Treatment compliance was checked at each visit by counting the capsules. The compliance was considered as:

- excellent: no day of missed treatment,
- good: <3 days of missed treatment,
- fair: from 3 to 7 days of missed treatment,
- poor: >7 days of missed treatment.

**Evaluation of Safety**

All adverse effects reported by the patients during the study period were recorded on the Case report form and classified in terms of type, time of onset, severity, duration and outcomeSubjects were made aware of possible side effects during the first visit.Blood parameters including Rheumatoid factor and C-reactive protein were assessed to rule out Rheumatoid Arthritis. Adverse reactions were monitored with health diaries, clinical interviews at visits 1, 4 and 12 weeks. Subjects were asked to report adverse events if any by phone.

**Statistical Methods**

The statistical analysis was carried out with SYSTA 12 version software. Chi-square test (qualitative variable) has been applied. The

efficacy of both the drugs was assessed individually using one way ANOVA repeated measure test and blood parameters with 2×2 ANOVA repeated measures test.Level of significance was set at ($P < 0.05$).

## Results

The pain score assessment by Lysholm knee scoring scale for individual drugs was as per Table – 1, 2.

**Efficacy Results (vide Table – 1, 2)**

The efficacyof the drugs was assessed mainly by thereduction in Osteoarthritic pain experienced by the patients. The degree of symptomatic joint pain was measured with the Lysholm knee scoring scale. An increase in the Lysholm knee score indicates the reduction in pain level.The mean pain score of both the drugs was evaluated.'One way ANOVA repeated measures test' shows significant P-value with reduction in the pain levels in both the groups maximal at the end of 12$^{th}$ week.

The significant P-value of the comparison between baseline and 1$^{st}$week, 1$^{st}$ to 4$^{th}$ week and 4$^{th}$ to 12$^{th}$ week ensures that both diacerein and SAMe are effective in reducing the pain level as assessed by "Repeated contrast test."

**Table - 1:** Mean and SD of pain score of the subjects who have received diacerein-week wise.

| Assessment | Mean | Std. Deviation | Onway ANOVA repeated measure F- value | p-value | Repeated contrast Test results | F value | p-value |
|---|---|---|---|---|---|---|---|
| Week 0 | 44.2 | 8.2 | 161.8 | <0.001 | Week 0 vs week 1 | 58.116 | 0.000 |
| Week 1 | 49.75 | 7.7 | | | Week 1 vs week 4 | 65.478 | 0.000 |
| Week 4 | 57.8 | 7.6 | | | Week 4 vs week 12 | 110.051 | 0.000 |
| Week 12 | 72.4 | 11.3 | | | | | |

Values were expressed as Mean ± SD in each group. Values differ significantly at $P \leq 0.05$. (One way ANOVA repeated measures test and repeated contrast test).

**Table - 2:** Mean and SD of pain score of the subjects who have received S- adenosylmethionine by week wise.

| Assessment | Mean | Std. Deviation | Onway ANOVA repeated measure F- value | p-value | Repeated contrast Test results | F value | p-value |
|---|---|---|---|---|---|---|---|
| Week 0 | 46.000 | 6.6178 | 201.790 | <0.001 | Week 0 vs week 1 | 77.075 | .000 |
| Week 1 | 51.000 | 5.9226 | | | Week 1 vs week 4 | 93.087 | .000 |
| Week 4 | 57.650 | 6.2205 | | | Week 4 vs week 12 | 174.666 | .000 |
| Week 12 | 68.025 | 6.8706 | | | | | |

Values were expressed as Mean ± SD in each group. Values differ significantly at $P \leq 0.05$. (One way ANOVA repeated measures test and repeated contrast test).

**Safety Results**

Mild to moderate diarrhea which was troublesome occurred in 12.5% in the diacerein group. Other GI side effects included abdominal pain 2.5% and dyspepsia of around 10% in the diacerein group. Only 7.5% and 2.5% in the SAMe group reported dyspepsia and gastritis respectively. Discolouration of urine was reported with Diacerein and mild to moderate hypersensitivity reactions were seen in few patients. Insomnia (7.5%) is one of the major adverse events which was observed in patients treated with SAMe. No

serious untoward event or adverse reactions occurred during the study. No clinically relevant differences were observed between any of the diacerein groups and the SAM group with regard to vital signs and clinical assessment parameters (**Table – 3, 4**).

**Table - 3:** Comparison of Adverse Effects in diacereinVs S-adenosylmethionine.

| **Adverse effects** | **Group** | | | | **Total** | |
|---|---|---|---|---|---|---|
| | **Diacerein** | | **S-adenosyl methionine** | | | |
| | **N** | **%** | **N** | **%** | **N** | **%** |
| Hypersensitivity reaction | 1 | 2.5 | 1 | 2.5 | 2 | 5.0 |
| Abdominal pain | 1 | 2.5 | 0 | .0 | 1 | 1.2 |
| Bowel motility disorder | 1 | 2.5 | 0 | .0 | 1 | 1.2 |
| Diarrhea | 5 | 12.5 | 0 | .0 | 5 | 6.2 |
| Dyspepsia | 4 | 10.0 | 3 | 7.5 | 7 | 8.8 |
| Gastritis | 0 | 0 | 1 | 2.5 | 1 | 1.2 |
| Nausea | 2 | 5.0 | 3 | 7.5 | 5 | 6.2 |
| Discolouration of urine | 2 | 5.0 | 0 | 0 | 2 | 5.0 |
| Insomnia | 0 | 0 | 3 | 7.5 | 3 | 7.5 |

**Table - 4:** Percentage of Adverse Effects in diacereinVs S-adenosyl methionine.

| **Adverse effects** | **Diacerein** | | **S-adenosyl methionine** | |
|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** |
| Present | 16 | 40.0 | 11 | 27.5 |
| Absent | 24 | 60.0 | 29 | 72.5 |

$\chi 2$ = 2. 40 P. value 0. 121 (NS)

**Table - 5:** Comparison of mean CRP levels between diacerein Versus S- adenosylmethionine in administered subjects.

| **Assessment** | **Group** | | | | **2 x 2 ANOVArepeated measure** | | |
|---|---|---|---|---|---|---|---|
| | **Diacerein** | | **S-adenosyl methionine** | | | | |
| | **Mean** | **SD** | **Mean** | **SD** | **Source** | **F value** | **P valve** |
| Week 0 | 11.80 | 12.15 | 8.750 | 11.0239 | Assessment | 13.130 | .001 |
| Week 12 | 5.17 | 2.43 | 6.450 | 1.9735 | Ass* drug | 3.083 | .083 |

Values were expressed as Mean ± SDin each group. Values differ significantly at P ≤ *0.05*(2x2 ANOVA repeated measures test)

**Table - 6:** Comparison of mean RA factor levels between diacerein Versus S- adenosylmethionine in administered subjects.

| **Assessment** | **Group** | | | | **2 x 2 ANOVA repeated measure** | | |
|---|---|---|---|---|---|---|---|
| | **Diacerein** | | **S-adenosyl methionine** | | | | |
| | **Mean** | **SD** | **Mean** | **SD** | **Source** | **F value** | **P valve** |
| Week 0 | 9.350 | 4.24 | 10.300 | 3.2597 | Assessment | .237 | .628 |

**Compliance**

Diacerein with a good compliance factor was less tolerable because of the incidence of diarrhea. SAMe though better tolerated has a compliance score of fair to good.

The mean CRP levels at week 0 and week 12 when compared to the two groups of diacerein and SAMe showed statistical significance of P-value<0.05, whereas the mean CRP levels, when compared within groups, is not statistically significant (**Table – 5**).

The mean RA factors at week 0 and week 12 when compared to the two groups of diacerein and SAMe shows no statistical significance in their effects both between groups and following comparison within groups (**Table – 6**).

## Discussion

This 12 week, prospective, randomized, Interventional study including 80 patients of both sexes, aged 45-70 years suffering from knee osteoarthritis, was designed to evaluate the clinical efficacy, compliance, and tolerability of diacerein Vs S-adenosyl methionine. This study suggests that daily administration of diacerein 50 mg/day allows a significant improvement, which was also noted on the administration of three daily capsules of SAMe. In the light of these results, some SYSADOA has a positive risk-benefit balance for patients with OA. As a matter of fact, diacerein and SAMe have demonstrated pain reduction and physical improvement in function using the Lysholm knee scoring scale (**Table – 1, 2**).

Evidence published by Osteoarthritis Society International(OARSI) indicated that diacerein had a greater effect on pain reduction in OA than analgesics like paracetamol [11]. Although NSAIDs have shown a more rapid onset of action than diacerein, the efficacy of drugs such as Diacerein on pain and joint function was comparable only after the first month of treatment.

In recent trends, there has been an increase in the use of symptomatic slow-acting drugs, connective tissue structure modifying agents like glucosamine or chondroitin sulfate and diacerein. Diacerein is an interleukin-1beta inhibitor. The cytokine interleukin-1beta plays a key role not only in cartilage degradation [12] but also in subchondral bone remodeling, chondrocyte apoptosis, and joint inflammation. Such drugs have a slow onset of efficacy and a longer carry-over effect once treatment is interrupted. S-adenosyl methionine is a dietary supplement used in the management of OA. It is known to reduce pain by increasing the synthesis of proteoglycans by human articular chondrocytes.

Regarding the adverse effects of diacerein, the most frequently reported were loose stools and diarrhea. Bartels, et al. [13] calculated that the risk ratio (RR) for developing diarrhea under diacerein versus placebo treatment was 3.51 (95% CI 2.55–4.83). Well in line with these meta-analyses, Rintelen, and co-authors [14] summarised that 39% of patients treated with diacerein versus 12% of patients receiving a placebo experienced at least one episode of loose stool or diarrhea.

Furthermore, lower GI symptoms decreased in most cases after prolonged treatment indicating tolerance to this effect.To minimise this risk, it is recommended to start diacerein treatment with half the prescribed dose (50 mg/day) for the first 2–4 weeks, the laxative properties of diacerein being dose-dependent [15]. Another major adverse effect reported with diacerein was discoloration of urine, due to the elimination of its metabolites, which is of no clinical significance. No incidence of upper GI effects such as gastric or duodenal ulcers was observed in the diacerein group indicating that diacerein does not inhibit COX and prostaglandins.

Nine clinical trials in Europe [16] and 1 in the United States [17] with a total of >22,000 participants have confirmedthe therapeutic activity of SAMe against osteoarthritis. Oral administration of SAMe (400 mg for 7 days) to 4 subjects significantly increased SAMe concentrations in synovial fluid by 3–4-fold compared with pre-treatment values [18]. With effects similar to NSAID's it is generally well tolerated, with adverse effects such as mild insomnia, loss of appetite,

constipation, nausea, dry mouth, sweating, dizziness, and restlessness [19]. Overalladverse effects were observed more in the diacerein group as compared to the SAMe group.

Dosing is one of the several factors affecting patient adherence to the treatment protocol. Reducing the frequency of dosing has been shown to improve patient compliance with medication regimens. Inaddition, several studies have shown that using single-dose regimens improves patient adherence [20]. Once- or twice-daily regimens are associated with better compliance than thrice-daily regimens [21]. We could then expect that the twice-daily dose of diacerein 50mg/day will improve patient's compliance compared to a regimen of three daily capsules of 200mg of SAMe. However, a study designed for this purpose exclusively may help in confirming this fact.Our study showed a better compliance of patients in the diacerein group than in the SAMe group.

Elevated levels of CRP present in early OA predicts the progression of the disease [22]. The reduction in CRP values (**Table - 4**) with Diacerein was found to be more statistically significant than SAMe indicating a potent anti-inflammatory action (IL-1) [6]. RA factor (**Table - 5**), however was not significantly elevated both between groups and within group.

This study highlights the fact that though both the SYSADOA, diacerein and SAMe are effective in relieving pain after treatment for more than a month,their tolerability and compliance vary widely. SAMe though better tolerated has a compliance score of fair to good. Diacerein with a good compliance factor was less tolerable because of the incidence of diarrhea.

## Conclusion

In conclusion, the benefit/risk ratio, indicate that the use of diacerein and S-adenosyl methionine could be ofpotential interest for the symptomatic management of OA. Both diacerein and SAMe were found to be effective in reducing the pain in Osteoarthritis patients. These drugs have a slow onset of action, with long term carryover effect and lesser side effects when compared to long term NSAIDS. But clinical trials focussing on their dose modification and duration of treatment would help rectify the issues relating to compliance and tolerability.

## References

1. Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V. The epidemiology of osteoarthritis of the knee in elderly patients living an urban area of Bangkok. J Med Assoc Thai, 2002; 85:154-61.
2. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through. Osteoarthritis Cartilage, January 2009; 18: 476-99.
3. Bruyere O, Burlet N, Delmas PD, Rizzoli R, Cooper C, Reginster JY. Evaluation of symptomatic slow-acting drugs in osteoarthritis using the GRADE system. BMC Musculoskeletal Disord., 2008; 9: 165.
4. Solignac M. Mechanisms of action of discern the first inhibitor of interleukin-1 in Osteoarthritis. Press Med., 2004; 33: S 10-2.
5. Moldovan F., Pelletier JP, Jolicoeur FC, CloutierJM, Martel-Pelletier J. Diacerein and rhein reduce the ICE-induced IL-1beta and IL-18 activation in human osteoarthritic cartilage. Osteoarthritis Cartilage, 2000; 8: 186-96.
6. Martin G, Bogdanowicz P, Domagala F, Ficheux H, Pujol JP. Rheininhibits interleukin-1beta-induced activation ofMEK/ERK pathway and DNA binding of NF-kappa B and AP-1 in chondrocytes cultured in hypoxia: a potential mechanism for its disease-modifying effect in

osteoarthritis. Inflammation, 2003; 27(4): 233–46.

7. Sanchez C, Mathy-Hartert M, Deberg MA, Ficheux H, ReginsterJY, Henrotin YE. Effects of rhein on human articular chondrocytesin alginate beads. Biochem Pharmacol., 2003; 65(3): 377–88.
8. Cantoni GL. The nature of the active methyl donor formed enzymatically from L-methionine and adenosine triphosphate. J Am Chem Soc., 1952; 74: 2942–3.
9. Agnoli A, Andreoli V, Casacchia M, Cerbo R. Effect of S-adenosyl-L-methionine (SAMe) upon depressive symptoms. J Psychiatr Res., 1976; 13: 43–54.
10. Barcelo HA, Wiemeyer JC, Sagasta CL, Macias M, Barreira JC. Effect of S-adenosylmethionine on experimental osteoarthritis in rabbits. Am J Med., 1987; 83: 55–9.
11. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthr Cartil., 2010; 18(4): 476–99.
12. Pelletier JP, Lajeunesse D, Reboul P, Mineau F, Fernandes JC, Sabouret P, et al. Diacerein reduces the excess synthesis of boneremodeling factors by human osteoblast cells from osteoarthritic subchondral bone. J Rheumatol., 2001; 28(4): 814–24.
13. Bartels EM, Bliddal H, Schondorff PK, Altman RD, Zhang W, Christensen R. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartil., 2010; 18(3): 289–96.
14. Rintelen B, Neumann K, Leeb BF. A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. Arch Intern Med., 2006; 166(17): 1899–906 (Erratum in: Arch Intern Med. 2007; 167(5): 444).
15. Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, et al. Efficacy and safety of diacerein in osteoarthritis of theknee: a double-blind, placebo-controlled trial. The Diacerein Study Group. Arthritis Rheum., 2000; 43(10): 2339–48.
16. Di Padova C. S-adenosyl methionine in the treatment of osteoarthritis.Review of the clinical studies. Am J Med., 1987; 83: 60–5.
17. Bradley JD, Flusser D, Katz BP, et al. A randomized, double-blind, placebo-controlled trial of intravenous loading with S-adenosyl methionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. J Rheumatol., 1994; 21: 905–11.
18. Stramentinoli G. Ademethionine as a drug. Am J Med., 1987; 83 (suppl): 35–42.
19. Hardy M, Coulter I, Morton SC, et al. S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease [Internet]. Rockville (MD): Agency for Healthcare Research and Quality(AHRQ): 2002 [cited 2011 Oct 29].
20. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther., 2001; 23: 1296-310.
21. Andrejak M, Genes N, Vaur L, Poncelet P, Clerson P, Carre A. Electronic pill-boxes in the evaluation of antihypertensive treatment compliance: comparison of once daily versus twice daily regimen. Am J Hypertens., 2000; 13: 184-90.
22. Spector TD.et al. Low level increase in serum, C-reactive protein are present in the early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum., 1997; 40: 723-7.